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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/666,267	09/21/2000	Peter S. Linsley	30436.11US06	1523

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	27

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/666,267	Applicant(s) LINSLEY
	Examiner GAMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 9/30/02, 9/8/03

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 87-93

4a) Of the above claim(s) 93 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 87-92

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on _____ is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☑ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4)☐ Interview Summary (PTO-413) Paper No(s). ____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 17

DETAILED ACTION

1. Applicant's communication filed 9/8/03, has placed this application in compliance with the Sequence Rules.

2. Applicant's amendment, filed 9/30/02, has been entered.
Claims 77-86 have been canceled. Claims 1-76 have been canceled previously.
Claims 89-93 have been added.

Newly submitted claim 93 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Newly submitted claim 93 is drawn to "an antibody produced by the method of claim 87 or 90", previously not claimed. Claim 93 drawn to antibody which is related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). Here, the anti-B7 antibodies can be made by a variety of in vitro and in vivo immunization procedures which employ differ ingredients and methods steps than that claimed. In addition, antibodies can be generated by various recombinant means.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 93 is withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Claims 87-92 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 9/30/02.
The rejections of record can be found in the previous Office Actions.

3. Upon reconsideration of applicant's amended claims and arguments, filed 9/30/02, have provided sufficient direction to the written support for the instant claims USSN 07/498,949, filed 3/26/90. In particular, USSN 07/498,949 provides for antibodies reactive to the CD28 ligand (B7) may be prepared using the CD28 ligand as immunogen, wherein said antibodies are reactive to the CD28 ligand can be reacted with B cells to inhibit T cell / B cell interactions (see page 11, paragraph 1 of USSN 07/498,949).

4. Formal drawings submitted 4/25/03 which comply with 37 CFR 1.84.

5. Applicant should amend the first line of the specification to update the status of the priority documents. USSN 08/219,200 is now U.S. Patent No. 6,641,809.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 88 stands rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed:

Claim 88. The method of claim 87, wherein the antibodies inhibit CD28 binding to B cells by at least approximately 30%.

While applicant's amendment, filed 9/30/02 has obviated the previous new matter rejection with respect to the previous recitation of claim 87, applicant's amendment fails to provide sufficient written description for the recitation of the method of claim 87, wherein the antibodies inhibit CD28 binding to B cells by at least approximately 30%.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed.

It appears that the claimed methods do not have written description in the specification as filed; therefore the claims represent a departure from the specification and claims as originally filed. Applicant's reliance on generic disclosure and possibly a single or limited species do/does not provide sufficient direction and guidance to the "features" currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06.

9. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

In view of the recitation of a B7 antigen having SEQ ID NO: 8", the previous rejection under 35 U.S.C. § 112, first paragraph, written description of the claimed invention, has been withdrawn.

10. It is noted that the claims are enabled for "B7 having SEQ ID NO: 8" or a "B7 fusion protein having SEQ ID NO: 8". However, this scope rejection is drawn to the "fragments of B7" as currently claimed.

Claims 87-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "a fragment of SEQ ID NO: 8" (see claim 87(a)(b) and 90) or "a fragment thereof" (see claims 87(a)(b) and 90(a)(b)" "which binds to CD28" or "B7Ig having SEQ ID NO: 8" does not reasonably provide enablement for any "a fragment of SEQ ID NO: 8" (see claim 87(a)(b) and 90) or "a fragment thereof" (see claims 87(a)(b) and 90(a)(b)" to be the specificity or to be employed as an immunogen in the instant claims or B7Ig in the absence of a sequence (see claim 91).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims. molecule

The instant specification (and the earliest priority document USSN 07/498.949) only provides sufficient direction and guidance on functional fragments of B7 comprising SEQ ID NO: 8, wherein said "fragment of SEQ ID NO: 8" (see claim 87(a)(b) and 90) or said "fragment thereof" (see claims 87(a)(b) and 90(a)(b)" "which binds to CD28" does not reasonably provide enablement for any "fragment of SEQ ID NO: 8" (see claim 87(a)(b) and 90) or "fragment thereof" (see claims 87(a)(b) and 90(a)(b)" to be the specificity or to be employed as an immunogen in the instant claims.

There is insufficient direction and guidance as to those B7 fragments which may used as immunogens that would provide the specificity to produce antibodies that react with B7 positive B cells and inhibit B cell interactions with CD28.

Although independent claim 90 recites "B7 antigen having SEQ ID NO: 8", claim 91 simply recites "wherein the B7 fusion protein is B7Ig". Claim 91 does not recite a SEQ ID NO: 8 or a source of B7Ig as recited in claim 92. Therefore, B7Ig requires the B7 having SEQ ID NO: 8 or the B7Ig fusion protein as deposited with ATCC as Accession Number 68627, and that the B7 antigen is the B-7/BB-1 antigen. See page 11, paragraphs 1 and 2 and page 13, paragraph 1 of the instant specification.

As pointed our previously, applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the "B7 antigen or antigenic fragment" as the immunogen or target specificity of the claimed methods. B7 or B7Ig may have some notion of the source of the antigen, however, claiming biochemical molecules by a particular name given to the protein (e.g B7 antigen) by various workers in the field fails to distinctly claim what that protein is and what it is made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "B7 fragment thereof or "B7Ig".

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

As pointed out previously, it was noted that Linsley et al. (PNAS 87: 5031-5035, 1990) discloses that homologs of CD28 and B7/BB-1 have not yet been identified in other mammalian species (see page 5035, column 1, last sentence).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any "B7 fragment thereof" or "B7Ig", yet the instant specification does not provide sufficient guidance and direction as to the structural features of said "B7 fragments" or "B7Ig" broadly encompassed by the claimed invention and the correlation between the chemical structure of B7 encoded by SEQ ID NO: 8 as supported by the specification as filed to the genus of "B7 fragments thereof" and "B7Ig", encompassed by the claimed invention. The reliance on the disclosed limited example(s) of B7 disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989) or of the B7Ig fusion proteins deposited with ATCC as Accession Number 68627 (see page 11, paragraphs 1 and 2 and page 13, paragraph 1 of the instant specification) does not support the scope of enablement for any "B7 antigen or antigenic fragment".

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands. Therefore, structurally unrelated or divergent B7 molecules or antigens encompassed by the claimed invention other than the B7 disclosed by Freeman et al. (J. Immunol. 143: 2714 -2722, 1989) or the B7Ig fusion proteins deposited with ATCC as Accession Number 68627 would be expected to have differences in their physicochemical properties or functional activities.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "B7 fragments" and "B7Ig" other than the "B7 fragments which bind CD28" or the B7Ig disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "B7 fragments" or "B7Ig" other than the "B7 fragments that bind CD28" or B7Ig having SEQ ID NO: 8 or encoded by the DNA as deposited as ATCC Accession NO. 68627 disclosed in the specification as filed as the target specificity or immunogen in the claimed methods

Without sufficient guidance, making and using "B7 antigens or antigenic fragments" other than the "B7 fragments" or "B7Ig" other than the "B7 fragments that bind CD28" or B7Ig having SEQ ID NO: 8 or encoded by the DNA as deposited as ATCC Accession NO. 68627 in the claimed methods would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Therefore, applicant is invited to amend the claims to recite "B7 fragments that bind CD28" or B7Ig having SEQ ID NO: 8 or encoded by the DNA as deposited as ATCC Accession NO. 68627 to obviate this rejection.

Also, applicant is invited to amend the claims to recite "said" rather "a" to provide proper and unambiguous antecedent basis for the dependent B7 fragments and B7Ig limitations.

Applicant has not provided sufficient guidance and direction to other methods of producing antibodies to B7 antigen, other than that indicated in the previous paragraph.

Applicant is invited to provide clear and distinct method steps and ingredients, which are supported by the written description of the specification as filed.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

11 Claims 87-92 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 87-92 are indefinite in their recitation as methods because the methods do not clearly set forth method steps and there is an absence of a resolution step, which reads back on the preamble of the claimed methods. The claims are indefinite because they merely recited a use without any active, positive steps delimiting how this use is actually practiced. Ex parte Erlich, 3 USPQ2d 1011 (CPAI 1986). See MPEP 2173.05(q). Applicant is invited to provide clear and distinct method steps and ingredients, which are supported by the written description of the specification as filed (and the earliest priority document USSN 07/498,949 to avoid prior art). It is noted that USSN 07/498,949 discloses the use of B7, B7Ig, or B7 fragments as immunogens.

B) Claim 88 lacks proper antecedent basis for "antibodies" in claim 87 which recites "antibody"..

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

12. Upon reconsideration of applicant's amended and newly added claims which appear to have priority back to USSN 07/498,949, filed 3/26/90, the prior art rejection under 35 U.S.C. § 103(a) as being unpatentable over Ledbetter et al. (U.S. Patent No. 5,182,368) in view of Linsley et al. (PNAS 87: 5031-5015, 1991) (1449) and Freeman et al. (J. Immunol. 143: 2714-2722, 1989) (1449) has been obviated.

The instant claims which required screening for antibodies that bind B7 positive B cells and inhibit B cell interaction with CD28 appear to be free of the prior art.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

After January 20, 2004, Phillip Gambel's telephone number will be (571) 272-0844 and Christina Chan's telephone Number will be (571) 272-0841.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
December 1, 2003